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14. ABSTRACT

Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials.

Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients' level of functional ability.

15. SUBJECT TERMS
None provided

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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Background: Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials.
Objective: Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients' level of functional ability.
Applicability: Well-designed CAT-PRO questionnaires can be used in both clinical trials and day-to-day clinical practice. For clinical trials, they provide researchers with the ability to put all patients, regardless of their functional abilities, together on the same scale. That means that one tool can be used to evaluate quality of life across many types of studies and many groups of patients, but that the results can still be compared. Those results can then also be compared to other clinical trial measures such as strength tests, timed function tests, or pulmonary function tests to help teach researchers and regulatory authorities about how "in clinic" tests commonly used in clinical trials relate to a persons' quality of life, and whether those tests are "clinically meaningful". In day-to-day clinical practice, it means that doctors can have a single tool that can give feedback on a patient's quality of life, even as their levels of ability change over time. Within 3 years, this project will be able to produce such a useful tool because much of the data has already been collected from the CINRG study and because the rest of the data will be from the large group of over 3000 volunteers who are already part of the Parent Project Muscular Dystrophy DuchenneConnect Registry.
Impact and Contributions: Data from the CINRG DMD natural history study cohort and the DuchenneConnect Registry will provide the basis for development of a "clinical trial-ready" novel CAT-based PRO measure that has been constructed against a background of comprehensive clinical assessments of strength and function across the DMD lifespan. This PRO measure will be rapidly usable as a sensitive measure for use in the growing field of DMD clinical trials, and will help to demonstrate "clinically meaningful" results to regulatory agencies in charge of new drug approval.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Duchenne muscular dystrophy
Person-reported outcomes
Health-related quality of life
Functional health assessment
UC Davis / CINRG Duchenne Natural History Study

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Aim 1: Development of ICF-based Item Banks from CINRG DNHS PRO Data (Year 1, Months 1-6) - We will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age). Data will include all available completed PRO form sets for all participants from the baseline visit up to at least the month 48 visit, and will an age range of 5-32+ years, which will represent approximately 1200+ 12-month intervals. Clinical data will include steroid treatment status, anthropometrics, timed motor performance testing (time to stand from supine, time to climb 4 stairs, time to run/walk 10 meters), Brooke and Vignos scales, and forced vital capacity pulmonary function. Some data from the cohort will be available out to 7 years of participation. At each visit time point, participants will be classified into a functional milestone group as previously described. Using that milestone grouping, we will evaluate 12-month change for each year of study participation. Those who increase in milestone scale score will be classified as having lost a functional milestone during that period. Participants will also be classified by steroid-user status as glucocorticoid naïve, previously-treated or currently-treated. Their questionnaire responses will be scored into instrument total and subscale scores per standard guidelines. Responses on all individual items will also be evaluated independently. Each instrument subscale and item will be classified according to ICF domain and subdomain for inclusion in domain-based item banks. Level of significance will be set at $p<0.05$.

Aim 1.1: Selection of Initial Item Bank Content (Year 1, Month 1-3) – Using all available PRO data, we will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age).

Task 1 **(COMPLETE)** – Human Subject Protection Approval Submission to DoD (Weeks 1-2): In collaboration with data management staff at the Cooperative International Neuromuscular Research Group, we will submit IRB approvals from sites engaged in the CINRG Duchenne Natural History Study (DNHS). The project is currently funded by DoD and site approvals have been obtained previously. As this portion of the project involves data analysis only, no additional research aims require addition to the original study protocol. Participants have already consented to collection and analysis of PRO data by the project PI and CINRG collaborators. DoD-specific consent language has been added as required and consent for project participation has been collected from participants. This subtask will be conducted by Dr. Henricson and Mr. de Bie.

Task 2 **(COMPLETE)** - Dataset curation and formatting (Weeks 3-4): In collaboration with data management staff at the Cooperative International Neuromuscular Research Group, we will reference the full-scale dataset from the CINRG Duchenne Natural History Study (DNHS) to construct an analysis-ready dataset including the functional milestone and PRO item responses required in the Aim 1 analysis. This subtask will be conducted by Dr. Henricson and Mr. de Bie.

Task 3 **(COMPLETE)** - PRO data analysis and WHO-ICF domain-based item bank construction (Week 4-Month 3): PRO instrument items will be evaluated to construct item banks based on the WHO-ICF domain structure. This subtask will be conducted by Dr. Henricson.

Aim 1.2 (Year 1, Month 4-5): To refine the item banks and ensure coverage across the entire spectrum of disease, we will identify ranges of function where overlapping PRO items or gaps in item content exist against a backdrop of the entire range of meaningful functional abilities demonstrated by the DMD population across all age groups.

Task 1 **(COMPLETE)** –Factor analysis and Rasch analysis to identify item bank performance (Months 4-5). Analysis for this aim will be conducted by Dr. Bagley, with the input and assistance of Dr. Henricson, Dr. McDonald and Dr.

Joyce.

Aim 1.3: Focus Groups to Develop Supplemental Domain Items (Year 3) **–** To address areas of overlap and gaps in item content, we will conduct focus group discussions with an expert advisory group of DMD clinical research professionals, health care providers, parent caregivers, and patients with DMD to identify relevant items for inclusion in a composite PRO measure, and to develop new items where suitable ones do not exist.

Task 1 **(COMPLETE)** – Human Subject Protection Approval Submission to DoD (Months 1-6): The project PI and co-investigators will develop a human subjects protocol and consent documentation for key informant interviews and focus groups, and will obtain IRB approval from UC Davis. UC Davis IRB approvals will be submitted to DoD HRPO for revision and approval. DoD revisions will be reviewed and approved by the UC Davis IRB. This task will be completed by Dr. McDonald, Dr. Henricson, Dr. Joyce and Mr. Owens.

Task 2 **(COMPLETE)** – Clinical expert key informant interviews (Month 6): Areas of overlap and gaps in item content will be discussed via teleconference with a group of DMD clinical experts to identify possible question content to supplement the existing item banks. This task will be conducted by Dr. Joyce and Dr. Henricson with the assistance of outreach coordinator Erica Goude.

Task 3 **(COMPLETE)** – Patient and Caregiver focus groups (Year 3 Months 1-9): Areas of overlap and gaps in item content will be discussed in small focus groups of DMD patients and parents/guardians in face-to-face meetings at the UC Davis Center for Neuromuscular Disease Research. This task will be conducted by Dr. Joyce and Dr. Henricson with the assistance of outreach coordinator Erica Goude.

Task 4 **(COMPLETE)** – Existing PRO item review and new item generation (Year 3 Month 9): The frequently mentioned and most relevant items will be compared to existing PRO tools to determine whether there are pre-existing question items that can be included in the item banks. Where none exist, new items will be developed and reviewed with focus group participants from Task 2 prior to inclusion. This task will be conducted by Dr. Joyce, Dr. McDonald, Dr. Mulcahey and Dr. Henricson.

AIM 2: Pilot Testing of WHO-ICF Domain Item Banks using DuchenneConnect (Year 4 Month 9)
DuchenneConnect is a web-based DMD patient data registry and epidemiology research tool hosted by Parent Project Muscular Dystrophy that is used by more than 3000 families worldwide to track important clinical data related to the health, function and health services utilization of their family member(s) with DMD. We will work with DuchenneConnect administrators to publish an online version of the full PRO banks including all final items across domains. We will ask DuchenneConnect participants to enroll in the study and complete question sets at baseline. One year later participants will be contacted by email and reminded to complete a follow-up set of assessments after 1 year of follow-up. Data will be combined with registry self-report glucocorticoid use and measures of functional "milestone" ability data.

Task 1 **(COMPLETE)** – Development of web-based item bank questionnaires (Year 3 Month 6): Using final pilot item banks developed in Aim 1, Dr. Henricson and Mr. Owens will work with PPMD DuchenneConnect representatives to construct a web-based version of item bank questionnaires and the related back-end database and accompanying data dictionary.

Task 2 – **(PENDING – November 20, 2017 Target Completion Date)** IRB review and approval of web-based DuchenneConnect item bank questionnaires (Year 3 Month 8): Dr. Henricson and Mr. Owens will coordinate IRB submission and review of web-based questionnaires and recruiting materials. This is a minimal risk study and can be processed at UC Davis via expedited IRB review.

Task 3 – **(PENDING – December 5, 2017 Target Completion Date)** Human Subject Protection Approval Submission to DoD (Year 3 Month 8): UC Davis IRB approvals will be submitted to DoD HRPO for revision and approval. DoD revisions will be reviewed and approved by the UC Davis IRB. This task will be completed by Dr. McDonald, Dr. Henricson, and Mr. Owens

Task 4 – Recruiting and launch of web-based forms in collaboration with DuchenneConnect (Year 4 Month 9): UC Davis outreach coordinator Erica Goude will collaborate with DuchenneConnect staff to provide email outreach and study recruiting to all participating DuchenneConnect members. This activity will continue until the end of Year 4.

Aim 2.1: Validation of New Domain-Based Item Banks (Year 4 Month 9) – Prospective 1-year data from the DuchenneConnect registry application of newly-derived item banks will be evaluated using techniques described in Aim 1 to confirm that items are responsive to self-reported changes in milestone ability over a time period consistent with design of contemporary clinical trials. Rasch analysis will be repeated to confirm item fit and performance for retained and newly-developed items.

Task 1 – Confirmatory Rasch Analysis (Year 4 Month 7): Item response data collected via DuchenneConnect will be tested to confirm responsiveness to changes in self-reported functional milestone abilities. Item responses for the draft item banks including new items directed to fill "gaps" will be re-analyzed by RASCH to confirm their item fit and performance. Dr. Bagley will conduct this activity, with input and data review by Dr. McDonald, Dr. Mulcahey, Dr. Joyce, and Dr. Henricson

Aim 2.2: Identification of Item Responsiveness to Group Differences Due to Glucocorticoid Therapy (Year 4 Month 7)Evaluate the responsiveness of the composite PRO item banks to differences in milestone scores. We will test the hypothesis that functionally-specific mobility and ADL PRO items will be differentially responsive functional "milestone" abilities.

Task 1 – Evaluation of responsiveness to differences functional "milestone" ability (Year 4 Month 7). Dr. Bagley and Dr. Henricson will conduct this activity, with input and data review by Dr. McDonald, Dr. Mulcahey, and Dr. Joyce.

AIM 3: Development of a Computerized Adaptive Testing PRO instrument for use in clinical trials (Year 4 Month 12):
In the fourth year of the project, we will use pilot data to develop a brief computerized adaptive testing (CAT) version of the new composite PRO instrument, and we will make it available to the clinical research community for inclusion in natural history studies and clinical trials for persons with DMD.

Aim 3.1: Perform a CAT simulation from data obtained from the comprehensive PRO item banks (Year 4). A real data simulation approach will be used to investigate the accuracy of each CAT generated from the full-item banks.

Task 1: Dr. Mulcahey will lead the group in developing CAT simulations for 5-, 10- and 15-item computer adaptive tests.

Aim 3.2: Establish discriminant and concurrent validity of the CAT version of the composite PRO in parents/ caregivers of DMD subjects (Year 4 Month 6 – Year 4 Month 12). Evaluation of the ability of the mobility and daily routines full-item banks and the 5-, 10-, and 15-item simulated CATs to discriminate between and among groups of DMD subjects.

Task 1 – IRB review and approval of CAT PRO simulations (Year 4 Month 6): Dr. Henricson and Mr. Owens will coordinate IRB submission and review of CAT simulation protocols and recruiting materials to enroll 80 DNHS participants at UC Davis. This is a minimal risk study and can be processed at UC Davis via expedited IRB review.

Task 2 – Human Subject Protection Approval Submission to DoD (Year 4 Month 6): UC Davis IRB approvals will be submitted to DoD HRPO for revision and approval. DoD revisions will be reviewed and approved by the UC Davis IRB. This task will be completed by Dr. McDonald, Dr. Henricson, and Mr. Owens

Task 3 – (Year 4 Month 7 – Year 4 Month 12): Dr. Mulcahey will lead the group in comparing results of newly-developed CAT evaluations to functional performance data collected on 80 DNHS participants enrolled at UC Davis in conjunction with their regularly scheduled study visits.

What was accomplished under these goals?

Aim 1: Development of ICF-based Item Banks from CINRG DNHS PRO Data (Year 1, Months 1-6) - We will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age). Data will include all available completed PRO form sets for all participants from the baseline visit up to at least the month 48 visit, and will an age range of 5-32+ years, which will represent approximately 1200+ 12-month intervals. Clinical data will include steroid treatment status, anthropometrics, timed motor performance testing (time to stand from supine, time to climb 4 stairs, time to run/walk 10 meters), Brooke and Vignos scales, and forced vital capacity pulmonary function. Some data from the cohort will be available out to 7 years of participation. At each visit time point, participants will be classified into a functional milestone group as previously described. Using that milestone grouping, we will evaluate 12-month change for each year of study participation. Those who increase in milestone scale score will be classified as having lost a functional milestone during that period. Participants will also be classified by steroid-user status as glucocorticoid naïve, previously-treated or currently-treated. Their questionnaire responses will be scored into instrument total and subscale scores per standard guidelines. Responses on all individual items will also be evaluated independently. Each instrument subscale and item will be classified according to ICF domain and subdomain for inclusion in domain-based item banks. Level of significance will be set at $p<0.05$.

Aim 1.1: Selection of Initial Item Bank Content (Year 1, Month 1-3) – Using all available PRO data, we will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age).

Accomplishments and Results: Results of our item responsiveness analysis are presented in detail in *Appendix 1: Initial Developlment of the Duchenne Muscular Dystrophy Lifetime Mobility Scale by Rasch Analysis* beginning with the *Results* section on Page 5 of 35 and continuing through the *Principle Components Analysis* section on Page 8 of 35.

Aim 1.2 (Year 1, Month 4-5): To refine the item banks and ensure coverage across the entire spectrum of disease, we will identify ranges of function where overlapping PRO items or gaps in item content exist against a backdrop of the entire range of meaningful functional abilities demonstrated by the DMD population across all age groups.

Accomplishments and Results: Results of our initial item bank evaluation are presented in Appendix 1 beginning on Page 8 of 35 under the *First-Pass Rasch Analysis* section and continuing to the top of Page 12 of 35. Selection of final model domains and refinement of those item banks for those domains via a second pass Rasch analysis is presented beginning on Page 12 of 35 and continuing through the *Revisions to Question Syntax and Response Structure* section which begins at the top of Page 23 of 35.

Aim 1.3: Focus Groups to Develop Supplemental Domain Items (Year 1 Month 9 - Year 3) **–** To address areas of overlap and gaps in item content, we will conduct focus group discussions with an expert advisory group of DMD clinical research professionals, health care providers, parent caregivers, and patients with DMD to identify relevant items for inclusion in a composite PRO measure, and to develop new items where suitable ones do not exist.

Accomplishments and Results: Input from the expert advisory group is described in the previously referred to section of Appendix 1 entitled *Grouping Question Items by WHO-ICF Domains* on Page 5 of 35 and the *Principle Components Analysis* section on Page 8 of 35. Additional input from our expert advisors resulted in the inclusion of question items reflecting tasks from various commonly-used clinical evaluations. These additional items are discussed in the section entitled *Comparable instruments from clinical practice; The North Star Ambulatory Assessment, Egen Klassifikation Scale and Performance of the Upper Limb (PUL) Assessment* beginning on Page 24 of 35. Data collection and evaluation was completed in August 2017. Results of this testing yielded parent/patient feedback regarding appropriate syntax for question items as well as additional items that address areas of the scales extending exhibiting ceiling and floor effects.

The resulting question set reflects activities that are relevant in daily patient activities and that span a larger range of mobility across the wide spectrum of disease progression. The investigator team also mapped each item to a corresponding clinical outcome measure item in the North Star Ambulatory Assessment, the EK Scale, and the PUL to facilitate cross-linking of data from clinical and PRO batteries and to ensure that the mobility constructs are similar and consistent for ambulation, trunk stability and movement, and upper limb function. The resulting item sets are attached as the field testing version of the DMD-LMS (see Appendix 2). Preparation of IRB/Human Subjects Protocols for field testing using the new instrument is underway with a completion target of November 20, 2017 for UC Davis IRB submission and December 5, 2017 for DoDHRPO submission.

AIM 2: Pilot Testing of WHO-ICF Domain Item Banks using DuchenneConnect (Year 2 Month 9 – Year 4 Month 9) **–** DuchenneConnect is a web-based DMD patient data registry and epidemiology research tool hosted by Parent Project Muscular Dystrophy that is used by more than 3000 families worldwide to track important clinical data related to the health, function and health services utilization of their family member(s) with DMD. We will work with DuchenneConnect administrators to publish an online version of the full PRO banks including all final items across domains. We will ask DuchenneConnect participants to enroll in the study and complete question sets at baseline. One year later participants will be contacted by email and reminded to complete a follow-up set of assessments after 1 year of follow-up. Data will be combined with registry self-report glucocorticoid use and measures of functional "milestone" ability data.

Aim 2.1: Validation of New Domain-Based Item Banks (Year 4 Month 4 – Year 4 Month 9) – Prospective 1-year data from the DuchenneConnect registry application of newly-derived item banks will be evaluated using techniques described in Aim 1 to confirm that items are responsive to self-reported changes in milestone ability over a time period consistent with design of contemporary clinical trials. Rasch analysis will be repeated to confirm item fit and performance for retained and newly-developed items.

Accomplishments and Results: As noted in the preceding section, construction of a web-based platform for instrument data collection has been completed using RedCap Online Survey resources provided by the UC Davis Clinical and Translational Science Center (CTSC). The system was developed during the initiation of activities in Specific Aim 1.3 to capture data during participant validation interviews, and operational details of the system are provided in the human subject study protocol in Appendix 2. Data collection will begin with the assistance of DuchenneConnect immediately upon approval of the human subjects protocol by UC Davis and the DoD. Once data collection is complete, we will conduct a final round of Rasch analysis-based question item calibration and will refine domain item list content to finalize the instrument's item lists.

Aim 2.2: Identification of Item Responsiveness to Group Differences Due to Glucocorticoid Therapy (Revised to Year 4 Month 7) – Evaluate the responsiveness of the composite PRO item banks to differences in milestone scores. We will test the hypothesis that functionally-specific mobility and ADL PRO items will be differentially responsive functional "milestone" abilities.

Accomplishments and Results: Using the data from the revised and calibrated item lists on completion of Aim 2.1, we will evaluate responsiveness of the DMD Lifetime Mobility Scale to differentiate between individuals with different levels of functional "milestone" ability. As proof of concept, we recently presented data to the World Muscle Society from the CINRG Duchenne Natural History Study using the POSNA Pediatric Orthopedic Data Collection Instrument (PODCI) where we demonstrated ability of mobility-related domain scores to differentiate between functional "milestone" groups. The POSNA PODCI mobility-related domain scores correlate with 6-minute walk test in ambulatory children and adolescents with Duchenne muscular dystrophy (DMD). Question items address ambulation, transfer and upper limb functional abilities, making the device suitable as an outcome measure in ambulatory and non-ambulatory groups. We compared 5 years of PODCI data from the UCD/CINRG DNHS cohort (n=410), representing >3000 observations from participants from <2-33 years of age. We assigned individuals to a functional "milestone" group representing level of function as previously described (Henricson, 2013). We evaluated items by ordered logistic regression to show differences between milestone groups. We constructed 1-year score differences to identify items that demonstrated change over that time in the group as a whole and in those who lost a functional milestone. 11/11 items in Transfers/Basic Mobility are sensitive to milestone group differences ($p<0.0001$) and show significant 1-year change ($p=0.05$- $p<0.0001$). 8/8 items in Upper Extremity Physical Function are sensitive to milestone group differences ($p<0.0001$) and show significant 1-year change ($p=0.05$- $p<0.0001$). 9/12 items in Sports/Physical Function are sensitive to milestone group difference ($p<0.0001$) and 8/9 milestone-sensitive items show significant 1-year change ($p=0.05$- $p<0.0001$). 1/5 items in Happiness is sensitive

to milestone differences ($p<0.0001$). No items in Pain/Comfort are sensitive to milestone differences or 1-year change. Domain scores derived from Transfer/Basic Mobility, Upper Extremity Physical Function, and Sports/Physical Function items are similarly responsive. We conclude that the POSNA PODCI instrument can be used in ambulatory and non-ambulatory DMD. A majority of mobility-related items and their derivative domain scores show differences between functional groups and changes over 1 year in ambulatory and non-ambulatory patients.

Reference: Henricson E, McDonald CM and the CINRG Investigators. Five-year longitudinal UC Davis CINRG Duchenne Natural History Study (DNHS) data show mobility-focused POSNA PODCI items are sensitive to 12-month disease progression across all stages of DMD functional ability. Neuromuscular Disorders, October 2015, Volume 25, Supplement 2.

AIM 3: Development of a Computerized Adaptive Testing PRO instrument for use in clinical trials (Year 4 Month 7 – Year 4 Month 12):
In the fourth year of the project, we will use Aim 2 pilot data to develop a brief computerized adaptive testing (CAT) version of the new composite PRO instrument, and we will make it available to the clinical research community for inclusion in natural history studies and clinical trials for persons with DMD.

Accomplishments and Results: The Cooperative International Neuromuscular Research Group recently transferred it's Coordinating Center from Children's National Medical Center to the Therapeutic Research in Neuromuscular Disorders Solutions (TRiNDS) group, also based in Washington, D.C. The CINRG Duchenne Natural History Study is launching an expanded version of the study that incorporated members of the E.U.-based Prosensa Duchenne Natural History Study (PRO-DMD) at an expanded network of centers worldwide. Plans are currently underway to include the instrument in the new study protocol as a computer-adaptive test for Aim 3 field testing, with data collection from a combined study cohort of up to 500 participants, with the total data collection cohort size be determined initially by use of English as the primary language. Development and approval of the human subject study protocol is slated for Spring of 2018 with data collection to occur during the Summer of 2018.

Aim 3.1: Perform a CAT simulation from data obtained from the comprehensive PRO item banks <u>(Year 4)</u>. A real data simulation approach will be used to investigate the accuracy of each CAT generated from the full-item banks.

Aim 3.2: Establish discriminant and concurrent validity of the CAT version of the composite PRO in parents/ caregivers of DMD subjects (Year 4 Month 6 – Year 4 Month 12). Evaluation of the ability of the mobility and daily routines full-item banks and the 5-, 10-, and 15-item simulated CATs to discriminate between and among groups of DMD subjects.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Results of Aim 1 activities have been presented in multiple conference proceedings and publications. We presented information on responsiveness of Person Reported Outcomes (PROs) in the CINRG Duchenne Natural History Study at the Duchenne Regulatory Sciences Consortium Workshop in April of 2016. Proceedings of the meeting were recently published in PLoS Currents (Larkindale et al, 2017) and are available to the public via PubMed Central (PMC5300692). Work on the relationship between disease-related functional milestones and pulmonary function characteristics over the lifespan was presented at the Parent Project Muscular Dystrophy Pulmonary Care Workshop (April 2106). The workshop was attended by disease experts, representatives of the pharmaceutical research industry and federal government funding and regulatory agencies. A workshop summary publication is currently under review by the *American Journal of Respiratory and Critical Care Medicine*. Two additional publications are in draft from the CINRG group and highlight the disease milestone concepts developed during Aim 1 of this project. The paper, titled *Time to event analysis for the loss of clinically-meaningful milestones in Duchenne muscular dystrophy: The effect of glucocorticoids throughout the lifespan* expands on functional milestone scale items as critical events to assess relative risks of disease progression in steroid-treated and steroid-naïve populations. The paper was accepted for publication by *Lancet* in September 2017.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, we will field-test the draft device as outlined in Aim 2 activities. Following field administration of the device, we will refine response scales using an iterative Rasch analysis approach and prepare the final device for distribution using a computer adaptive testing design.

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  As previously noted, publications include the following:

  1. Larkindale J, Abresch RT, Aviles E, Bronson A, Chin J, Furlong P, Gordish-Dressman H, Habeeb-Louks E, Henricson E, Kroger H, Lynn C, Lynn S, Martin D, Nuckolls G, Rooney W, Romero K, Sweeney L, Vandenborne K, Walter G, Wolff J, Wong B, McDonald CM and the members of the Duchenne Regulatory Science Consortium, Imaging-DMD Consortium and the CINRG Investigators. Duchenne regulatory science consortium meeting on Duchenne disease progression and progression modeling. PLoS Curr. 2017 Jan 12:9.
  2. McDonald CM, Henricson E, Abresch RT, Duong T, Joyce NC, Hu F, Clemens PR, Hoffman EP, Cnaan A, Gordish-Dressman H and the CINRG Investigators. Time to event analysis for the loss of clinically meaningful milestones in Duchenne muscular dystrophy: The effect of glucocorticoids throughout the lifespan. *LANCET, In Press.*
  3. McDonald CM, Gordish-Dressman H, Henricson E, Duong T, Joyce N, Leinonen M, Hu F, Cnaan A, Abresch RT and the CINRG Investigators. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history study with and without glucocorticoids. Neuromuscular Disorders, *Submitted.*
  4. Finder J, Mayer OH, Sheenan D, Sawnani H, Abresch RT, Benditt J, Birnkrant D, Duong T, Henricson E, Kinnett K, Connolly AM, McDonald CM. Pulmonary endpoints in Duchenne muscular dystrophy: a workshop summary. *Am J. Resp. Crit. Care Med, In Press*

  Books or other non-periodical, one-time publications.

1. Henricson EK, McDonald CM, Mayhew A, Bagley A, Joyce N, Oskarsson B, Sodeberg-Miller L, Liu S, Abresch R and the CINRG Investigators. Finding clinical meaning in patient-reported functional health: Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale. World Muscle Society, October 2017. St. Malo, France.
2. McDonald CM, Gordish-Dressman H, Henricson EK, Duong T, Joyce N, Jhawar S, Leinonen M, Hu F, Connolly A, Cnaan A, Abresch RT and the CINRG Investigators. Longitudinal Pulmonary Function Testing Outcome Measures in Duchenne Muscular Dystrophy: Long-term Natural History with and without Glucocorticoids. World Muscle Society, October 2017. St. Malo, France.
3. McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce N, Hu F, Clemens PR, Hoffman EP, Cnaan A, Gordish-Dressman H and the CINRG Investigators. Long-term Benefits of Glucocorticoids in Duchenne Muscular Dystrophy—Is It Worth It? World Muscle Society, October 2017. St. Malo, France.
4. McDonald CM, Gordish-Dressman H, Henricson E, Abresch RT, Cnaan A. Steroid use delays but does not prevent loss of pulmonary function in patients with Duchenne muscular dystrophy (DMD). Annual meeting of the American Thoracic Society, May 2017. Washington, DC.

Other publications, conference papers and presentations.

2017, Summer **Invited Speaker, UC Davis Precision Medicine Symposium:** PRECISION MEDICINE AND MUSCULAR DYSTROPHY: Similarities and synergies between human and canine models Lecture Title: Wearables, PROs and person- generated health data. Davis, CA

2017, Summer **Keynote Speaker, Parent Project Muscular Dystrophy Drug Development Roundtable**
Lecture Title: *Finding clinical meaning in patient-reported functional health:Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale* Parent Project Muscular Dystrophy Annual Meeting Chicago, IL

2017, Spring **Invited Presenter, Duchenne Regulatory Sciences Consortium Annual Meeting**
Lecture Title: Finding clinical meaning in patient-reported functional health:
Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale.
Critical Path Institute, D-RSC, Washington, DC

2017, Winter **Invited Presenter, Muscular Dystrophy Association Annual Scientific Meeting**
Lecture Title: Finding clinical meaning in patient-reported functional health:
Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale.
Muscular Dystrophy Association, Washington, DC

2017, Winter **Invited Presenter, UC Davis Genomic Medicine Human Genomics Seminar Series**
CME Lecture Title: Measuring and predicting mobility change over the lifespan in Duchenne muscular dystrophy: Genotype, clinical phenotype and patient-reported ability.
UC Davis School of Medicine, Sacramento, CA

- **Website(s) or other Internet site(s)**

  Nothing to Report

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**

  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Craig McDonald, MD (PI) - No Change

Name: Erik Henricson, MPH (Co-Investigator) - No Change
Name: Nanette Joyce, DO (Co-Investigator) - No Change
Name: Anita Bagley, PhD, MPH (Co-Investigator) - No Change
Name: Corey Owens, MS (Data Manager) – No Change
Name: Erica Goude, MS (Outreach Coordinator) - No Change
Name: Mary Jane Mulcahey, PhD (Co-Investigator) – No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

1. **DMD-LMS Rasch Technical Report**
2. **Revised DMD-LMS Questionnaire**
3. **Cross-Linked DMD-LMS Questionnaire**
4. **List of Changes from Draft DMD-LMS Questionnaires**